#12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Technology Transfer, Inc.
Zuhal Fahim

Patent No.: 5,070,080

Issue Date: December 3, 1991

Patent Title: METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM

Mail Stop PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Your Applicant, TECHNOLOGY TRANSFER, INC. and ZUHAL FAHIM, represent that they are owners of United States patent No. 5,070,080 granted to MOSTAFA S. FAHIM, on December 3, 1991 for METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM. TECHNOLOGY TRANSFER, INC. is the Assignee of the entire interest in and to said patent in the field of chemical sterilization of male pet animals (dogs and cats). ZUHAL FAHIM is successor in interest to MOSTAFA S. FAHIM as to the remainder of the patent. Your Applicant acting through the undersigned attorney, hereby proffers this application for extension of patent term under 35 USC 156 by submitting the following information required by 37 CFR 1.740. An original of the Power of Attorney is attached hereto as Appendix A.

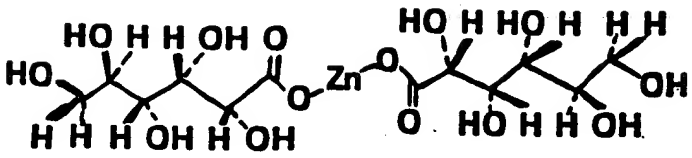
1. **Identification of Approved Product**

The approved product is zinc gluconate neutralized by arginine in the veterinary drug NEUTERSOL® Injectable Solution. The active ingredient is zinc as zinc gluconate. Zinc gluconate is a chemical compound otherwise known as

Chemical Name: Bis(D-gluconato-O^1,O^2)zinc.

CAS Number: CAS-4468-02-4

Chemical Structure:



Molecular Formula: $C_{12}H_{22}O_{14}Zn$

Molecular Weight: 455.69

Further details concerning the approved product are presented in the FDA approved package insert for that product, a copy of which is attached as Appendix B.

2. Federal Statute and Applicable Provision Under Which Regulatory Approval Occurred.

Section 512 of the Federal Food, Drug and Cosmetic Act (21 USC 360(b); FDC Act).

3. Date Permission Received For Commercial Marketing and Use

Technology Transfer, Inc. first received permission for commercial marketing and use of zinc gluconate neutralized by arginine under Section 512 of the Federal Food, Drug and Cosmetic Act (21 USC 360(b)) on March 17, 2003.

4. Identification of Active Ingredient in Drug Product and Statement That It Has Not Been Previously Approved For Commercial Marketing or Use Under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

The active ingredient of NEUTERSOL® Injectable Solution is zinc as zinc gluconate. Zinc gluconate neutralized by arginine has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. Statement That the Application Is Being Submitted Within the 60-Day Period Permitted For Submission and the Last Day On Which the Application Can Be Submitted.

This application for patent term extension is being submitted pursuant to 37 CFR 1.720(f) within sixty (60) days of the date zinc gluconate neutralized by arginine received permission for marketing. The last day on which this application could be submitted is May 16, 2003.

6. Identification of Patent For Which Extension Is Being Sought.

Patent No.: 5,070,080
Name of Inventor: Mostafa S. Fahim
Issue Date: December 3, 1991
Expiration Date: December 3, 2008

7. Copy of Patent.

A copy of the patent identified in paragraph 6 hereof is attached as Appendix C.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments and Re-examination Certificates.

No disclaimers have been made, certificate of correction or re-examination certificates issued with respect to U.S. patent No. 5,070,080. All maintenance fee payments have been made for U.S. patent No. 5,070,080. A copy of confirming letters issued by the U.S. Patent and Trademark Office as to the payment of the three maintenance fees is attached as Appendix D.

9. Copy of Assignment of Patent to Applicant.

Technology Transfer, Inc. is the assignee of Mostafa S. Fahim of U.S. patent No. 5,070,080 (serial No. 303,747, filed January 30, 1989) in the field of chemical sterilization of male pet animals (dogs and cats). The approved product is for use in male dogs for achieving sterility/infertility by intratesticular injection and is

within the aforesaid field of use. The assignment was recorded on May 9, 2003 in reel 013634 starting at frame 0511. A copy of the recorded assignment is attached as Appendix E.

Zuhal Fahim is successor in interest to Mostafa S. Fahim as to the balance of U.S. patent No. 5,070,080 by assignment by Zuhal Fahim as Personal Representative of Mostafa S. Fahim to Zuhal Fahim as an individual. The assignment was recorded on May 13, 2003 in reel 013645 starting at frame 0252. A copy of the recorded assignment is attached as Appendix F.

10. **Statement That Patent Claims the Method of Using the Approved Product and Demonstration That Applicable Patent Claims Read on the Methods of Use.**

U.S. Patent No. 5,070,080 claims the active ingredient zinc as zinc gluconate in the approved product zinc gluconate neutralized by arginine for use in inhibiting generation, maturation, motility or viability of sperm. Claim 1 reads as follows:

> 1. A method of inhibiting generation, maturation, motility or viability of sperm in a reproductive tract of an animal comprising applying in said reproductive tract an aqueous solution of a mineral gluconate salt and an amino acid capable of forming the solution, said aqueous solution neutralized to a pH in the range of 6.0 to 7.5 and applied in an amount effective to inhibit generation, maturation, motility or viability of sperm in the reproductive tract and said mineral gluconate salt and said amino acid being present in substantially equal molar amounts at a concentration in the range from about 0.05M to about 2.0M.

The approved product is a sterile solution containing 0.2M zinc gluconate and 0.2M L-arginine in water adjusted to pH 7 with hydrochloric acid for intratesticular injection in male dogs. Zinc gluconate is one specific example of a mineral gluconate salt. L-arginine is one specific example of an amino acid capable of forming the solution. The zinc gluconate and the L-arginine are present in substantially equal molar amounts and at a concentration in the range from about 0.05M to 1.0M. The pH is adjusted within the range from about 6 to 8. When the approved product is injected into a male dog (i.e., an animal having a reproductive tract), the Injection

Solution causes sterility/infertility in the dog (i.e., inhibits generation, maturation, motility or viability of sperm in the reproductive tract). Claim 1 therefore reads on use of the approved product for the approved purpose.

Claim 2 reads as follow:

2. The method of claim 1 wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.05M to about 0.3M.

Claim 2 adds to claim 1 the limitation that the concentration of the mineral gluconate salt (e.g., zinc gluconate) and the amino acid (e.g., arginine) be present at a concentration between about 0.05M and about 0.3M. Claim 2 reads on use of the approved product for the approved purpose.

Claim 3 reads as follows:

3. The method of claim 1 wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.1M to about 0.2M.

Claim 3 adds to claim 1 the limitation that the mineral gluconate salt and amino acid have a concentration between about 0.1M to about 0.2M. The approved product is within this range.

Claim 3 therefore also reads on use of the approved product for the approved purpose.

Claim 4 reads as follows:

4. The method of claim 1 wherein the mineral gluconate salt is zinc gluconate.

Claim 4 adds to claim 1 the limitation that the mineral gluconate salt be zinc gluconate. The active ingredient in the approved product is zinc as zinc gluconate and Claim 4 therefore reads on use of the approved product for the approved purpose.

Claim 5 reads as follows:

> 5. The method of claim 4 wherein the amino acid is a basic amino acid selected from the group consisting of lysine, arginine, histidine and mixture thereof.

Claim 5 adds to claim 4 the limitation that the amino acid be selected from a group, inter alia including arginine, the amino acid used in the approved product. Claim 5 therefore reads on use of the approved product for the approved purpose.

Claim 6 reads as follows:

> 6. A method of inhibiting generation or maturation of sperm in a testis or epididymis of a male animal comprising applying in said testis or epididymis an aqueous solution of zinc gluconate and an amino acid capable of forming the solution, said aqueous solution neutralized to a pH in the range of 6.0 to 7.5 and applied in an amount effective to inhibit generation or maturation of sperm in the testis or epididymis and said zinc gluconate and said amino acid being present in substantially equal molar amounts at a concentration in the range from about 0.05M to about 2.0M.

The approved product is a solution for intratesticular injection for achieving sterility/infertility in male dogs. This comprises treating a male animal (e.g., dog) having a testis or epididymis with an aqueous solution containing zinc gluconate and an amino acid capable of forming the solution (e.g., arginine)
for the purpose of inhibiting generation or maturation of sperm in the testis or epididymis (e.g., inducing sterility/infertility). The approved product has a pH of 7 and contains zinc gluconate neutralized by arginine with the zinc gluconate and arginine in substantially equal molar amounts and in the concentration range. Claim 6 therefore reads on the approved use of the approved product.

Claim 7 reads as follows:

> 7. The method of claim 6 wherein the concentration of the zinc gluconate and the amino acid is from about 0.05M to about 0.3M.

Claim 7 adds to claim 6 a limitation regarding the molar concentration of the zinc gluconate and amino acid, the approved product being in the stated range. Claim 7 therefore reads on the approved use of the approved product.

Claim 8 reads as follows:

> 8. The method of claim 6 wherein the concentration of the zinc gluconate and the amino acid is from about 0.1M to about 0.2M.

Claim 8 adds to claim 6 a limitation regarding the molar concentration of the zinc gluconate and amino acid, the approved product being in the range. Claim 8 therefore also reads on the approved use of the approved product.

Claim 9 reads as follows:

> 9. The method of claim 6 wherein the amino acid is a basic amino acid selected from the group consisting of lysine, arginine, histidine and mixtures thereof.

Claim 9 adds to claim 6 the limitation that the amino acid used in the process be selected from a group, inter alia, including arginine which is the amino acid used in the approved product. Claim 9 therefore reads on the approved use of the approved product.

Claim 10 reads as follows:

> The method of claim 9 wherein the basic amino acid is arginine.

Claim 10 adds to claim 9 and has the requirement that the amino acid specifically be arginine which is the amino acid used in the approved product. Claim 10 reads on the approved use of the approved product.

11. **Relevant Dates During Regulatory Review.**

Relevant dates and information pursuant to 35 USC 156(g) to enable the Examiner of Health and Human Services to determine the applicable regulatory review period are as follows:

Technology Transfer, Inc. submitted an Investigational New Animal Drug (INAD) application on July 24, 1991 and the Center for Veterinary Medicine (CVM) assigned INAD number 8349 on November 14, 1991. A copy of the CVM's letter assigning the INAD number is attached as Appendix G. On February 6, 2003 the CVM indicated that the final step was complete for the purpose of recommending approval of a New Animal Drug Application (NADA).

On February 10, 2003, Technology Transfer, Inc. submitted an NADA and on March 17, 2003 NADA 141-217 A0000 of NEUTERSOL® (zinc gluconate neutralized by arginine) Injectable Solution for chemical sterilization was approved for marketing in the United States. A copy of the CVM's letter approving the NADA is attached as Appendix H.

12. **Brief Description of Activities Undertaken By Applicant During the Applicable Regulatory Period With Respect to the Approved Product and the Significant Dates Applicable to Such Activities.**

A brief description of the development activities undertaken by Technology Transfer, Inc. during the applicable regulatory review period with respect to zinc gluconate neutralized by arginine and significant dates applicable to such activities are attached herewith as Appendix F and is a chronology of major communications between Technology Transfer, Inc. and the FDA's Center for Veterinary Medicine between July 24, 1991 and March 17, 2003.

13. **Applicant's Opinion As to Why the Patent is Eligible for Patent Extension and How the Length of Extension Was Determined.**

Applicant believes that U.S. patent No. 5,070,080 is eligible for an extension under 35 USC 156 because it satisfies all of the requirements for such extension including, inter alia, the following:

(a) 35 USC 156(a):

U.S. patent No. 5,070,080 claims a method of treatment with a "product" that is a "new animal drug" as defined by the statute [35 USC 156(f)(2) and PTO Rules 37 CFR 1.710(b)(2)] to mean not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques, including any salt or ester of the active ingredient zinc as zinc gluconate, as a single entity or in combination with another active ingredient.

(b) 35 USC 156(a)(1):

The term of U.S. patent No. 5,070,080 has not expired prior to submission of the application for extension.

(c) 35 USC 156(a)(2) and 37 CFR 1.720(b):

The term of U.S. patent No. 5,070,080 has never been extended.

(d) 35 USC 156(a)(3):

This application for extension is submitted by the owners of record of U.S. patent No. 5,070,080 in accordance with the requirements of 35 USC 156(d) and 37 CFR 1.710.

(e) 35 USC 156(a)(4):

The approved product zinc gluconate neutralized by arginine was subject to regulatory review prior to its commercial marketing or use.

(f) 35 USC 156(a)(5)(A)

Permission for the commercial marketing or use of the product, zinc gluconate neutralized by arginine, after the regulatory review period is the first commercial marketing or use of the product (zinc gluconate neutralized by arginine) under the provisions of the FDC Act (21 USC 360(b)) under which such regulatory period matured.

(g) 35 USC 156(c)(4):

No other patent has been extended for the same regulatory review period for the product zinc gluconate neutralized by arginine.

Length of Extension

The length of extension of the patent term of U.S. patent No. 5,070,080 claimed by Applicant is five (5) years.

The regulatory review period exceeds five (5) years and is shown by the following:

(a) The period of review under 35 USC 156(g)(4)(B)(i), hereinafter the INAD period, was from November 14, 1991 (effective date of INAD) until February 10, 2003 (NADA submission date), which is 4,106 days or 11.2 years.

(b) The period of review under 35 USC 156(g)(4)(B)(ii), hereinafter the NADA period, was from February 10, 2003 (NADA submission date) until March 17, 2003 (NADA approval date), which is 35 days or 0.1 years.

(c) The total regulatory period under 35 USC 156(g)(4) was 4,141 days or 11.3 years.

(d) Applicant acted with due diligence during the entire period of regulatory review and therefore the noted term of eligible extension under 35 USC 156(c) should not be shortened for lack of due diligence.

(e) Under 35 USC 156(C)(2) the period of extension includes only one-half of INAD period determined under 35 USC 156(g)(1)(B)(i), i.e., 2,053 days or 5.6 years. In the absence of limitations noted above, the period of term extension for U.S. patent No. 5,070,080, taking into account the deduction of one-half of the INAD period, would have been 2,088 days or 5.7 years.

(f) Under 35 USC 156(g)(6)(A) the length of extension of the patent terms of U.S. patent No. 5,070,080 is limited to five (5) years.

(g) In compliance with 35 USC 156(c)(3) the period remaining in the term of U.S. patent No. 5,070,080 after NADA approval of zinc gluconate neutralized by arginine (i.e, from March 17, 2003 to December 3, 2008 is 2,088 days or 5.7 years which added to the five (5) years of extension is 10.7 years and therefore is not in excess of fourteen (14) years.

14. Acknowledgement of Duty of Disclosure

Applicant acknowledges a duty to disclose to the Commissioner for Patents and Secretary of Health and Human Services any information which is material to the determination to be made relative to this application for extension.

15. Fee

The prescribed fee for receiving and acting upon this application for extension is enclosed herewith. If additional fees are due, they may be charged to deposit account 06-1090.

16. The Name, Address and Telephone Number of the Person to Whom Inquiries and Correspondence Relating to the Application for Patent Term Extension Are to Be Directed.

Grace J. Fishel
11970 Borman Drive, Suite 220
St. Louis, MO 63146
Telephone: (314) 878-0440
Fax: (314) 275-7693

17. Certified Duplicate of Application.

A duplicate copy of the Application papers certified as such is enclosed.

18. Declaration.

The declaration set forth in 37 CFR 1.740(b) for Patent Term Extension under 35 USC 156 is attached as Appendix J.

Respectfully submitted,

(314) 878-0440

(Mrs.) Grace J. Fishel
Reg. No. 25,864

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Mailing Label Number: EF113850525US

Date of Mailing: May 15, 2003

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" mail under 37 CFR 1.10 on the date indicated above in an envelope addressed to: Mail Stop PATENT EXTENSION, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Grace J. Fishel

APPENDIX A

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Technology Transfer, Inc.

Patent No.: 5,070,080

Issue Date: December 3, 1991

Patent Title: METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM

Commissioner for Patents
Mail Stop PATENT EXTENSION
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY

Technology Transfer, Inc., a corporation organized and existing under the laws of Missouri with registered agent and address of Don L. Landers, 33 E. Broadway, Suite 190, Columbia, Missouri 65203-4290, and Zuhal Fahim, an individual residing at 1634 Marshall, Houston, Texas 77006-4122, being the joint owners of record of the above identified U.S. patent, hereby appoint Grace J. Fishel as our attorney with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to her at the mailing address and telephone number hereafter given:

Name:	Grace J. Fishel
Registration No.:	25,864
Address:	11970 Borman Drive, Suite 220
	St. Louis, MO 63146
Telephone No.:	(314) 878-0440
Fax No.:	(314) 275-7693

TECHNOLOGY TRANSFER, INC.

Zuhal Fahim

By: Zuhal Fahim
Title: President

ZUHAL FAHIM

Zuhal Fahim

Zuhal Fahim

APPENDIX B

NEUTERSOL® Injectable Solution

(Zinc Gluconate Neutralized by Arginine)
Chemical Sterilant

Caution: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

NEUTERSOL® Injectable Solution

(Zinc Gluconate Neutralized by Arginine)
Chemical Sterilant

Caution: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Sterile intratesticular injectable aqueous solution containing 0.2 M zinc gluconate neutralized to pH 7.0 with 0.2 M L-arginine (13.1 mg zinc per milliliter).

Active Ingredient:

Each mL contains
Zinc as Zinc Gluconate ..... 13.1 mg

Other Ingredients:

L-Arginine ..... 34.8 mg
Water for Injection ..... q.s.
HCl to adjust to pH 7

INDICATIONS

Neutersol® Injectable Solution is indicated for chemical sterilization in 3 to 10 Month old male dogs.

DOSAGE AND ADMINISTRATION

Food should be withheld for 12 hours prior to injection to help prevent vomiting.

The drug is administered as one injection per testicle. Dose is based on testicular width (See Table 1) and is determined by measuring each testicle at its widest point using the caliper provided.

Table 1: Dose Corresponding to Testicular Width

Range of Testicular Width (mm)	Dose Administered mL
10-12	0.2
13-15	0.3
16-18	0.5
19-21	0.7
22-24	0.8
25-27	1.0

Testicular Measurement and Injection Procedure
Observe the proper testicular measurement and injection technique as demonstrated in the Neutersol® Injection Procedure video.

Testicular Measurement:

1. Check to see that the caliper is clean.
2. With the dog lying on its back, measure the width of each testicle by placing the testicle inside the two measuring points and then slide the ruler until it rests gently against the testicle.
3. Read the dose corresponding to the measurement by noting the position of the indicator line on the sliding ruler. If the indicator line exceeds the dosage line, use the next higher dose (See Diagram A).
4. The testicle is too small for injection if the indicator line does not fall on or below the minimum position marked on the caliper (See Diagram B).
5. The testicle is too large for injection if the indicator line falls beyond the maximum position for the 1.0 mL dose marked on the caliper (See Diagram C).

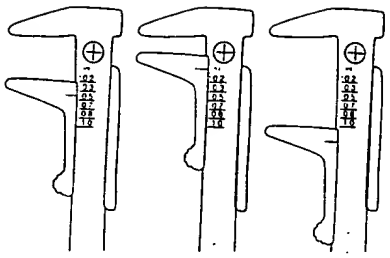


Diagram A **Diagram B** **Diagram C**

Injection Procedure:

1. Chemical restraint should be considered to prevent the dog from moving during injection (See **Warnings**).
2. Use two syringes — one syringe for the dog's right testicle and one syringe for the dog's left testicle. Each testicle should be injected with a separate sterile needle. **Use a 1 cc U-100 insulin syringe with 28 gauge, 1/2-inch needle for injection of Neutersol®.** Larger gauge needles may cause drug to leak from the injection site (See **Warnings**).
3. Position the dog so that it is lying on its back for testicular measurement and intratesticular injection.
4. Use the caliper provided to measure the width of **each** testicle at the widest point and determine the dose for each testicle (See Testicular Measurement).
5. Withdraw into each syringe the correct dose of Neutersol® to be injected into each testicle according to testicular measurement.
6. Prepare the scrotum with an appropriate disinfectant. Avoid use of alcohol as it irritates the scrotal skin of some dogs.
7. Hold the testicle firmly in one hand (do not squeeze) and use the other hand to hold the syringe filled with the dose for that testicle. Pull the skin tightly over each testicle to avoid injection into the scrotal sac or into the scrotal skin (See **Warnings**). Insert the needle into the dorsal cranial portion of the testicle beside the caput (head) epididymis (See Diagram D).
8. Inject slowly. Rapid injection may stimulate contraction of the seminiferous tubules and cause drug to leak from the injection site (See **Warnings**).
9. Do not use excessive injection pressure to force the drug into the testicle. If resistance is felt, discontinue the injection immediately. Do not re-inject. Neutersol® cannot be safely used in this dog.
10. Repeat the procedure for the remaining testicle. It is recommended as standard procedure to inject the left testicle first and then the right testicle to avoid confusion and re-injecting the same testicle.

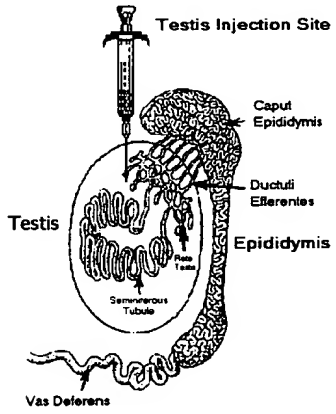


Diagram D

CONTRAINDICATIONS

Do not use Neutersol® in dogs with:

- Undescended testicles (cryptorchid).
- A disease or malformation of the testicle (including fibrosis of the testicles or epididymides).
- A history of allergic reaction to any of the components of the drug.
- Pre-existing scrotal irritation or dermatitis.

WARNINGS

Human Warnings: Keep this and all drugs out of the reach of children. Not for human use. Wash the skin with soap and water and flush eyes with copious amounts of water if contact occurs. Flush mouth with water and drink plenty of water if accidental ingestion occurs. Contact a physician in cases of accidental exposure by any route (oral, dermal, or injection).

Animal Safety Warnings: Proper injection technique and post injection care are critical to the safe use of Neutersol®.

Do not inject Neutersol® into the scrotal sac or scrotal skin. Contact between the drug and the scrotal skin activates collagenase enzymes, which may result in scrotal irritation, dermatitis, ulceration or necrosis. Chemical restraint should be used, if necessary, to prevent the dog from moving during the injection. To avoid leakage of drug from the injection site use only a 28 gauge 1/2-inch needle, inject slowly and immediately stop the injection if you feel resistance. Do not attempt to re-inject Neutersol® if you feel resistance to the injection. If you suspect that the drug was injected improperly into the scrotal sac or has contacted the scrotal skin, the dog

should be closely monitored for up to 7 days post-injection for local adverse reactions.

Do not allow dogs to bite or lick the scrotum after injection. Monitor dogs closely while in the veterinary facility and for at least 7 days following release from the veterinary facility for signs of scrotal inflammation. Leash walk only and do not allow the scrotum to contact hard, wet surfaces as this may result in irritation, dermatitis, ulceration or necrosis. Distribute the Client Information Sheet to each client for proper care post-injection.

Do not inject Neutersol® more than once into each testicle.

PRECAUTIONS

1. To avoid irritation to the scrotal skin, do not shave or clip the scrotal hair. Use a nonalcoholic disinfectant as an aseptic agent.
2. Use this product only in healthy male dogs following a thorough examination of the scrotum to ensure the scrotum is free of skin irritation and ulceration and that both testicles are descended and normal as determined by digital palpation by the examining veterinarian.
3. The safety and effectiveness of Neutersol® has not been established in dogs less than 3 Months of age or in dogs greater than 10 Months of age.
4. Do not use if the testicular width is less than 10 mm or greater than 27 mm.
5. Obtain an accurate measurement of testicular widths by using the caliper provided and the dose corresponding to testicular measurement. Both testicles must be injected with the appropriate dose using the correct procedure in order to minimize adverse reactions and achieve sterility.
6. In dose determination and field studies, the most serious cases of scrotal irritation and ulceration occurred as a result of improper injection technique or were associated with the dog biting or licking the injection site after release to the owner. Detailed instructions on proper care post-injection should be provided to the owner via the attached Client Information Sheet (CIS).

ADVERSE REACTIONS

In a field study with 270 dogs, Neutersol® caused both local adverse reactions at the injection site and systemic reactions (See Table 2).

Neutersol® injection was observed to be painful in 2.6% of 270 treated dogs. Six dogs vocalized and one dog kicked following injection. Apparent scrotal pain post-injection was the most commonly reported local reaction (6.3%), most frequently seen during the first two days post-injection.

The most commonly reported systemic reactions to the Neutersol® injection were neutrophilia (6.3%), vomiting (4.4%), anorexia (4.1%) and lethargy (2.2%). These reactions were typically seen within 7 days of the injection. However, vomiting was most commonly seen on the day of the injection, between 1 minute and 4 hours post-injection. Six of 10 dogs that vomited did so more than once during this period. Withholding food for 12 hours prior to injection may prevent this from occurring.

The most severe reactions occurred when dogs bit or licked the scrotum following injection (See **Warnings**). These severe reactions were seen in < 1% of 270 dogs. One dog was returned to the clinic on Day 3 for an ulcerated scrotum. The wound healed with medical therapy. The second dog was reported with a perforated scrotum and a severe scrotal infection on Day 17 post-injection. The dog had licked and chewed through the scrotum down to the testicle. Surgical castration and scrotal ablation were performed.

Table 2: Adverse Reactions

Adverse Reactions	No. of Animals (n = 270)	Percent (%)
Reaction Upon Injection		
Vocalization	6	2.2%
Kicking	1	0.4%
Local Reactions		
Scrotal Pain*	17	6.3%
Scrotal Irritation	3	1.1%
Biting and Licking	2	0.7%
Scrotal Swelling	2	0.7%
Scrotal Irritation and Dermatitis	2	0.7%
Scrotal Ulceration	1	0.4%
Scrotal Infection	1	0.4%
Dry Scrotal Skin	1	0.4%
Scrotal Bruising	1	0.4%
Preputial Swelling	1	0.4%
Scrotal Sore	1	0.4%
Systemic Reactions		
Neutrophilia	17	6.3%
Vomiting**	12	4.4%
Anorexia	11	4.1%
Lethargy	6	2.2%
Diarrhea	5	1.9%
Leukocytosis	2	0.7%

*Most scrotal pain was reported on the first two days after injection.
**Ten of the 12 dogs vomited within 1 minute and 4 hours after the injection.

To report a suspected adverse reaction, call 1-877-638-8377.

INFORMATION for OWNER or PERSON TREATING ANIMALS

Transient testicular swelling is an expected reaction to the injection. Field and dose determination data indicate that the swelling begins 24 hours post-injection and peaks at 48 hours post-injection. By 1 Month post-injection, most testicles will be atrophied. However, the degree of atrophy will vary individually and there may be variability between the left and right testicles of the same dog. This should be considered an expected response to the injection.

Neutersol® may not kill sperm present at the time of injection. Therefore, keep treated dogs away from females in heat for at least 60 days post-injection.

Unlike surgical castration, dogs treated with Neutersol® become sterile without removal of the testicles and, therefore, testosterone is not completely eliminated. Diseases which occur as a result of or in conjunction with testosterone hormones (prostatic disease, testicular or perianal tumors) may not be prevented.

As with surgical castration, secondary male characteristics (roaming, marking, aggression, or mounting) may be displayed.

CLINICAL PHARMACOLOGY

Neutersol® is a necrotizing agent that has a local effect when injected into the testicle. Based on histopathology, one or more of the following events occur after injection of Neutersol®.

- Atrophy of the testicles, epididymides, seminiferous tubules, and prostate gland.
- Scar tissue formation which prevents movement of sperm from the seminiferous tubules to the epididymis.

EFFECTIVENESS

The effectiveness of Neutersol® was evaluated in a field study of 270 male dogs of various breeds between 3 – 10 Months of age. Of the 270 dogs that started the study, 224 completed the study to Month 6 and were included in the effectiveness evaluation.

Semen analyses[1] were conducted at 2, 6, and 12 Months post-injection. Dogs had to be aspermic[2], azoospermic[3], necrospermic[4], or oligospermic[5] at the Month 6 evaluation to be considered a treatment success. One injection of Neutersol® in each testicle produced successful chemical sterilization in 223/224 dogs.

One treatment failure occurred in the field study. The Month 6 semen analysis for one dog revealed 100% motility and a sperm concentration of 165 million. Two dogs that were sterile at Month 6 and, therefore, deemed treatment successes, had sperm at month 12. One dog was azoospermic at Month 6 but at Month 12 was oligospermic (19 million sperm) with 100% motility. The second dog was oligospermic (10 million sperm) with 50% motility at Month 6, but at Month 12 had a sperm concentration of 49 million with 80% motility.

In a dose determination study, 30 male Beagle dogs, 6 Months of age, were injected with Neutersol® and followed for 2 years. Ten dogs were treated with a placebo. All dogs were exposed to untreated females in heat during the first 12 Months. Seven out of the 10 dogs in the control group mated with the females and 100% of these matings resulted in pregnancy. In the Neutersol®-treated dogs, up to 40% mated with the females and 0% resulted in pregnancy. Two Neutersol®-treated males, the only treated males with sperm in the ejaculate from Months 12-24, mounted the females but no pregnancies resulted. One female was artificially inseminated using one of the dog's semen but a pregnancy did not result.

[1]Normal Semen Values:
Sperm concentration: 200-1000 X 10^6/ejaculate
Semen volume: 1-40 mL/ejaculate
Spermatozoa motility >70% with progressive forward motility
[2] Aspermia = No semen ejaculated
[3] Azoospermia = No sperm in the ejaculate
[4] Necrospermia = Sperm in the ejaculate are motionless/dead
[5] Oligospermia = Sperm concentration less than 20 X 10^6 (for purposes of this field study)

Mean serum testosterone levels were 41% to 52% lower in the groups treated with Neutersol® compared to the control group throughout the dose determination study. However, there were dogs in all treated groups that had testosterone levels similar to those for the control dogs at Months 1, 3, 6, and 9 and from 12 to 24 months post-injection. By Month 24, the testosterone levels for all but nine of treated dogs were in the same range as control dogs.

ANIMAL SAFETY

Twenty-four Beagle dogs were assigned to 4 groups (6 dogs/group) and were injected with placebo or 1X, 1.5X or 2X the recommended dose (volume) of Neutersol® in each testicle on days 0 and 14. The following adverse injection site reactions were displayed: mild discomfort when sitting down after the first injection (1X, 1.5X and 2X), difficulty walking 24 hours after the first injection (1 dog in the 2X group), swelling at 24-48 hours after the first and second injections (1X, 1.5X, 2X) and scrotal pain at 24 hours after the second injection (2X). There was an increase in resistance to the injection as the volume administered increased and as the size and consistency of the testicles changed in the 1X group after the first injection.

Six of the dogs developed scrotal irritation, dermatitis or necrosis post-Neutersol® injection. Two of these dogs developed mild scrotal irritation (1.5X group) or dermatitis (2X group) within 3 days of first and second injections, respectively. Four dogs (1X, 1.5X, 2X) developed more serious scrotal lesions (scrotal dermatitis with purulent discharge and necrosis), including one dog that required surgical castration due to necrosis of approximately one-half of the scrotal length. These more serious adverse reactions were observed from 24 hours to 8 days post-injection (in 2 dogs after the first injection and in 2 dogs after the second injection). These lesions occurred in 2 dogs that moved during the injection procedure, 1 dog with a pre-existing scrotal skin lesion and 1 dog where the injection was administered despite strong resistance to the injection. Housing conditions post-injection (wet, cement flooring) were also considered a contributing factor in the development of the scrotal lesions (See **Warnings**).

STORAGE: Store at controlled room temperature 15-30°C (59-86°F).

HOW SUPPLIED: NEUTERSOL® Injection is supplied in 2 mL sterile vials.

U.S. Patent Nos. 4,937,234; 5,070,080

Manufactured by:
Meridian Medical Technologies, Inc.
Columbia, MD 21046 U.S.A.
for: Technology Transfer, Inc.
Columbia, MO 65203 U.S.A.
Distributed by:
Addison Biological Laboratory, Inc.
Fayette, MO 65248 U.S.A

0001056

APPENDIX C

United States Patent [19]

Fahim

[11] **Patent Number: 5,070,080**

[45] **Date of Patent: Dec. 3, 1991**

[54] **METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM**

[76] Inventor: **Mostafa S. Fahim**, 500 Hulen Dr., Columbia, Mo. 65203

[21] Appl. No.: **303,747**

[22] Filed: **Jan. 30, 1989**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 230,582, Aug. 10, 1988, Pat. No. 4,937,234.

[51] **Int. Cl.**[5] **A61K 31/715**; A61K 31/415; A61K 31/315; A61K 31/195

[52] **U.S. Cl.** **514/53**; 514/400; 514/494; 514/561; 514/564; 514/565

[58] **Field of Search** 514/970, 561, 53, 356, 514/365, 423, 494, 400, 564, 565; 424/641, 642, 643

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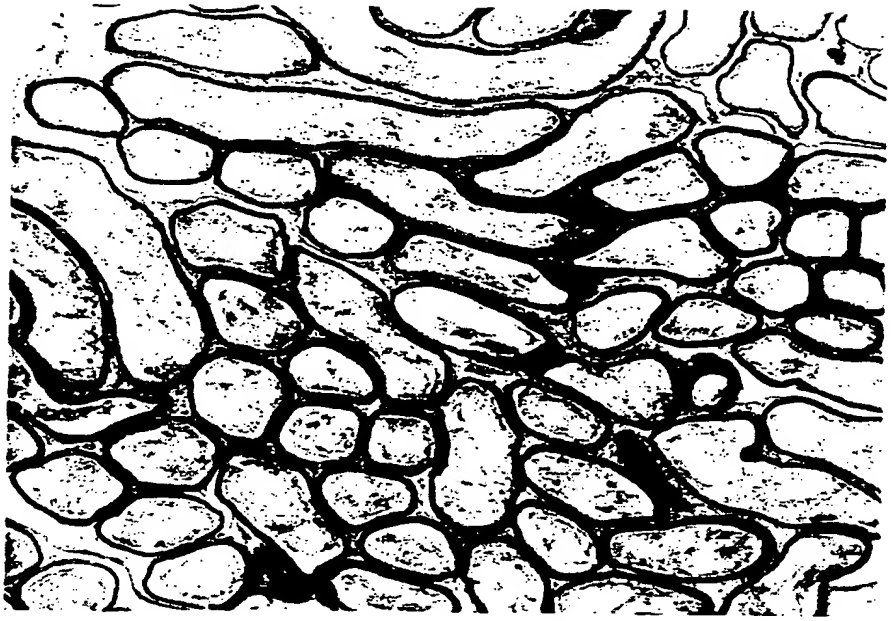
[57] **ABSTRACT**

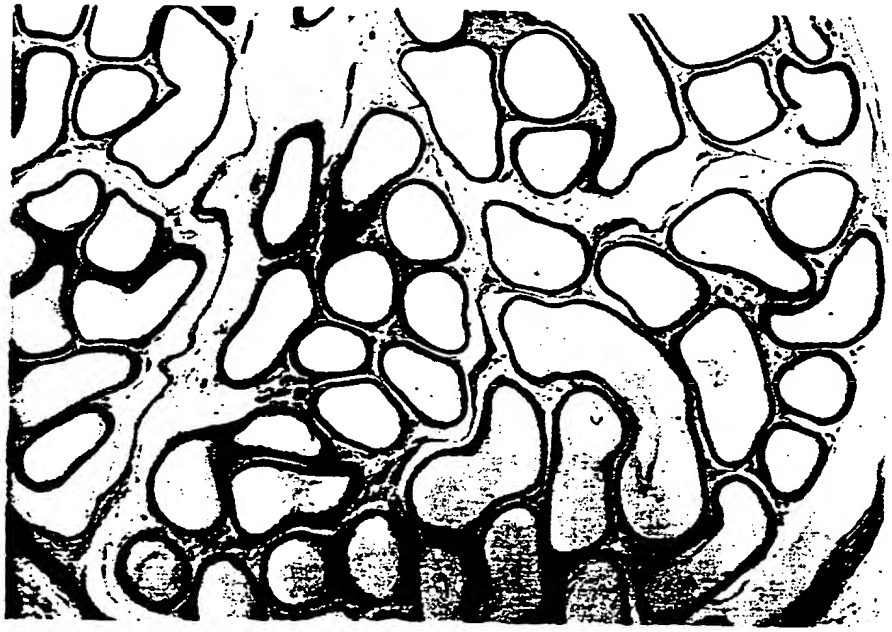
A cell permeable physiologically acceptable water soluble mineral salt of a carboxylic acid such as zinc acetate, calcium acetate, zinc gluconate and the like having a pH in the range of 6.0 to 7.5 capable of forming a stable solution under ambient conditions at pH 7.0 is bioavailably effective at inhibiting the generation, maturation, motility and viability of sperm when applied to sperm or developing sperm in the testis, epididymis or vas deferens of a male subject or the vagina, cervix, uterus or fallopian tubes of a female subject. When the subject is a male subject and the mineral salt is zinc gluconate or the like and is injected into the testis or epididymis, the stability and efficacy of the mineral salt at pH 7.0 is improved by the presence of an amino acid such as arginine which acts as a permeation enhancer.

15 Claims, 1 Drawing Sheet



CONTROL EPIDIDYMIS

FIG. 1



TREATED EPIDIDYMIS WITH
0.05 ML ZINC GLUCONATE
+ ARGININE 0.1M

FIG. 2

METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM

This application is a continuation-in-part of application Ser. No. 230,582, filed Aug. 10, 1988, for Minerals in Bioavailable Form which is now U.S. Pat. No. 4,937,234.

BACKGROUND OF THE INVENTION

The present invention relates to a method of contraception and compositions useful therefor that are applicable to males and females wherein the generation, maturation, motility and viability of sperm is affected by direct application of minerals in bioavailable form to the sperm or developing sperm in the target organ. Direct application of minerals in bioavailable form avoids the side effects found with other methods which rely on hormones or from the passage of a drug through the digestive tract.

Various water soluble minerals are toxic to sperm and have been injected into the testis or epididymis and been found effective at inhibiting the generation or maturation of sperm in the seminiferous or epididymal epithelium. They have also been found effective in vitro at inhibiting sperm motility and viability and postulated as a vaginal, cervical, uterine or tubal contraceptive in females. These methods, however, have not been put into commercial use because of certain adverse side effects.

To avoid adverse side effects in vivo, lower levels of less toxic materials are clearly preferred. To be effective and avoid hurting the subject, however, such materials must be in a form which is physiologically acceptable and cell permeable. Most water soluble minerals such as zinc chloride, zinc sulfate, zinc tannate and the like have proved too acidic to be commercially acceptable and cannot be neutralized with sodium hydroxide or sodium bicarbonate without effecting the stability of the solution or introducing an unacceptable level of sodium or other counterion.

In view of the above, it is an object of the present invention to provide a class of cell permeable physiologically acceptable water soluble minerals which are effective at inhibiting generation, maturation, motility and viability of sperm when applied in the testis, epididymis or vas deferens or in the vagina, cervix, uterus or fallopian tubes and which are not too acidic, caustic or astringent to cause discomfort to the subject. Other objects and features will be in part apparent and in part pointed out hereinafter. The invention accordingly comprises the methods and compositions hereinafter described and equivalents thereof, the scope of the invention being indicated by the subjoined claims.

SUMMARY OF THE INVENTION

A cell permeable physiologically acceptable water soluble mineral salt of a carboxylic acid having a pH in the range of 6.0 to 7.5 and capable of forming a stable solution under ambient conditions at pH 7.0 is bioavailably effective at inhibiting the generation, maturation, motility and viability of sperm when applied to sperm or developing sperm in a male or female reproductive track. In some instances, the stability and efficacy of the mineral salt at pH 7.0 is improved by the presence of an amino acid such as the basic amino acids arginine, lysine and histidine which acts as a permeation enhancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a histology photograph of an epididymal section from a control animal; and,

FIG. 2 is a histology photograph of an epididymal section from an animal treated in accordance with the present invention in Example 1.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention a cell permeable physiologically acceptable water soluble mineral is applied to sperm or developing sperm in the testis, epididymis or vas deferens of a male subject or the vagina, cervix, uterus or fallopian tubes of a female subject in an effective amount for inhibiting generation, maturation, motility or viability of the sperm. When applied to the epididymis, the mineral salt does not affect the production of testosterone and therefore does not influence the subject's secondary sex characteristics or libido. In the testis, on the other hand, the mineral decreases testosterone production at higher concentrations. Suitable materials for this purpose are mineral salts of a carboxylic acid having a pH in the range of 6.0 to 7.5 and capable of forming a stable solution under ambient conditions at pH 7.0. Physiologically acceptable minerals include zinc, calcium, iron, magnesium, manganese and the like and illustrative mineral salts include zinc acetate, calcium acetate and the mineral salts of a carboxylic acid derivative of a pentose or hexose such as zinc gluconate or zinc gulonate.

Depending on the target organ, the stability and efficacy of the mineral salt is improved in the presence of an amino acid. With zinc gluconate, it has been discovered that it can be neutralized in the presence of the following amino acids: alanine, valine, isoleucine, proline, glycine, serine, threonine, asparagine, glutamine, lysine, arginine, histidine and mixtures thereof. The adjustment cannot be made with cysteine, tyrosine, aspartic acid or glutamic acid and among the basic amino acids, arginine is preferred when zinc gluconate is injected into the testis or epididymis.

In neutralizing the mineral salts such as zinc gluconate, it is preferred that the mineral salts and the amino acid be present in substantially equimolar amounts. Suitable formulations for inhibiting the generation, maturation, motility and viability of sperm are formed with a molar ratio of mineral salt such as zinc gluconate to amino acid such as arginine from about 0.05M:2.0M to about 2.0M:0.05M, preferably from about 0.05 M:0.3 M to about 0.3M:0.05M and most preferably from about 0.1 M:0.2 M to about 0.2M:0.1 M and neutralized to a pH in the range from about 6.0 to about 8.0, preferably from about 6.5 to about 7.5 and most preferably 7.0.

When the biologically active mineral salt is near neutral in water solution without neutralization, such as zinc acetate and calcium acetate, the salts are effectively present in an amount from about 0.05M to about 2.OM, preferably from about 0.05M to about 0.3M and most preferably from about 0.1 M to about 0.2M.

In some instances, it is advantageous to administer the cell permeable physiologically acceptable water soluble minerals in a sustained release form. In such case they may be combined with polymers or microspheres formed of aloe vera muccopolysaccharides or the like as a vehicle to make the compound long-acting for cervi-

cal and uterine contraception and to enable the mixture to adhere to the fallopian tubes for fallopian tube contraception.

Cell permeable physiologically acceptable water soluble minerals have the potential of being a post-coital method of contraception by diffusing them into the uterus through the vagina with microspheres providing for sustained release for 4–5 days after coitus. Since fertilization and implantation usually requires about 5 days, a compound having such properties can stop implantation of the fertilized egg and be a major breakthrough in the field of fertility control.

The following examples illustrate the invention.

EXAMPLE 1

Twenty-five sexually mature male rats were divided into the following five groups:

1. Control
2. Injected intratesticularly with 0.1 M (5%) Zinc Gluconate
3. Injected intratesticularly with 0.1 M (1.46%) L-Lysine
4. Injected intratesticularly with 0.1 M (5%) Zinc Gluconate and 0.1 M (1.46%) L-Lysine
5. Injected intratesticularly with 0.1 M (5%) Zinc Gluconate and 0.1 M (1.74%) Arginine

After sixty days, the animals were sacrificed and body, testis, epididymis and prostate weights determined. The results are shown in Tables I–VI. Histology photographs were also made of testicular sections. The treatment applied in Group 5 produced the most significant change in decreasing the size of the reproductive organs. The results also show that arginine is a better permeation enhancer for zinc gluconate in the testis than lysine.

TABLE I

		% WEIGHT DECREASES FROM CONTROL		
Group	pH	TOTAL TESTIS	TOTAL EPIDIDYMIS	PROSTATE
Group 2 - Rats Injected with 0.1M (5%) Zinc Gluconate	5.5	68.98	45.10	25.67
Group 3 - Rats Injected with 0.1M (1.46%) L-Lysine	7.4	20.49	16.16	23.31
Group 4 - Rats Injected with 0.1M (5%) Zinc Gluconate and 0.1M (1.46%) L-Lysine	7.0	67.97	47.92	25.67
Group 5 - Rats Injected with 0.1M (5%) Zinc Gluconate and 0.1M (1.74%) Arginine	7.0	80.50	58.35	43.40

TABLE II

GROUP 1
CONTROL RATS
(Weight in Grams)

Animal	Final	Testicle Weights			Epididymis Weights				
No.	body Weight	Right	Left	Total	Right	Left	Total	S.V.	Prostate
254	501	1.648	1.684	3.332	0.588	0.617	1.205	0.774	1.514
255	470	1.706	1.740	3.446	0.638	0.609	1.247	0.757	1.706
256	608	1.972	2.050	4.022	0.680	0.631	1.311	0.690	1.490
257	524	1.755	1.729	3.484	0.636	0.686	1.322	0.812	1.616
258	516	1.774	1.705	3.479	0.675	0.614	1.289	0.826	1.291
X	523.8	1.771	1.782	3.553	0.643	0.631	1.275	0.772	1.523
S. D.	51.4	0.122	0.152	0.270	0.037	0.032	0.048	0.054	0.156
S. E.	23.0	0.055	0.068	0.121	0.017	0.014	0.022	0.024	0.070

TABLE III

GROUP 2
RATS INJECTED WITH 0.1M (5%) ZINC GLUCONATE
(Weight in Grams)

Animal	Final	Testicle Weights			Epididymis Weights				
No.	Body Weight	Right	Left	Total	Right	Left	Total	S.V.	Prostate
234	578	0.504	0.585	1.089	0.340	0.295	0.635	0.512	1.102
235	544	0.324	0.761	1.085	0.332	0.338	0.670	0.549	1.080
236	499	0.235	0.451	0.686	0.200	0.245	0.445	0.271	0.701
237	563	0.930	0.713	1.643	0.522	0.499	1.021	0.561	1.496
238	532	0.436	0.575	1.011	0.330	0.398	0.728	0.601	1.280
X	543.2	0.486	0.617	1.103	0.345	0.355	0.700	0.499	1.132
S. D.	30.3	0.269	0.123	0.344	0.115	0.098	0.209	0.131	0.293
S. E.	13.6	0.120	0.055	0.154	0.051	0.044	0.093	0.059	0.131

TABLE IV

GROUP 3
RATS INJECTED WITH 0.1M (1.46%) L-LYSINE
(Weight in Grams)

Animal	Final	Testicle Weights			Epididymis Weights				
No.	Body Weight	Right	Left	Total	Right	Left	Total	S.V.	Prostate
239	555	1.577	1.462	3.039	0.557	0.533	1.090	0.557	1.035
240	516	1.501	1.452	2.953	0.557	0.542	1.099	0.504	1.142
241	555	1.513	1.529	3.042	0.571	0.599	1.170	0.750	1.477
242	520	1.448	1.313	2.761	0.590	0.457	1.047	0.612	1.027
243	465	1.137	1.327	2.464	0.454	0.485	0.939	0.505	1.160
X	522.2	1.435	1.417	2.825	0.546	0.523	1.069	0.586	1.168
S. D.	37.0	0.173	0.093	0.245	0.053	0.055	0.085	0.102	0.183
S. E.	16.5	0.077	0.042	0.110	0.024	0.025	0.038	0.046	0.082

TABLE V

GROUP 4
RATS INJECTED WITH 0.1M (5%) ZINC GLUCONATE
AND 0.1M (1.46%) L-LYSINE
(Weight in Grams)

Animal	Final	Testicle Weights			Epididymis Weights				
No.	Body Weight	Right	Left	Total	Right	Left	Total	S.V.	Prostate
244	588	0.484	0.565	1.049	0.237	0.319	0.556	0.518	1.158
245	548	0.667	0.437	1.104	0.320	0.305	0.625	0.647	1.266
246	498	0.516	0.582	1.098	0.330	0.271	0.601	0.557	0.864
247	539	0.382	0.899	1.281	0.326	0.476	0.802	0.792	1.271
248	548	0.669	0.487	1.156	0.372	0.366	0.738	0.651	1.100
X	544.2	0.544	0.594	1.138	0.317	0.347	0.664	0.633	1.132
S. D.	32.1	0.124	0.180	0.089	0.049	0.080	0.102	0.106	0.166
S. E.	14.3	0.055	0.081	0.040	0.022	0.036	0.046	0.047	0.074

TABLE VI

GROUP 5
RATS INJECTED WITH 0.1M (5%) ZINC GLUCONATE
AND 0.1M (1.74%) ARGININE
(Weight in Grams)

Animal	Final	Testicle Weights			Epididymis Weights				
No.	Body Weight	Right	Left	Total	Right	Left	Total	S.V.	Prostate
249	480	0.180	0.254	0.434	0.153	0.104	0.257	0.088	0.247
250	520	0.344	0.145	0.489	0.280	0.240	0.520	0.341	0.777
251	501	0.387	0.311	0.698	0.206	0.238	0.444	0.380	0.830
252	562	0.492	0.480	0.972	0.395	0.399	0.794	0.603	1.571
253	519	0.324	0.550	0.874	0.311	0.330	0.641	0.442	0.884
X	576.4	0.345	0.348	0.693	0.269	0.262	0.531	0.371	0.862
S. D.	139.5	0.113	0.166	0.234	0.094	0.111	0.203	0.187	0.472
S. E.	62.4	0.051	0.074	0.105	0.042	0.050	0.091	0.084	0.211

EXAMPLE 2

Ten sexually mature male rats were injected intra-epididymally into the head of the epididymis with 0.05 ml of a solution composed of 0.1 M (5%) zinc gluconate and 0.1 M (1.74%) arginine neutralized with hydrochloric acid to pH 7.0. The ten treated animals were examined for changes in testicular function. Spermatogenesis was normal and there was no significant change in testosterone blood levels. Each treated male was mated with five female rats but no pregnancy occurred.

The animals were sacrificed and histology photographs were taken of epididymal sections from the treated animals, a typical one of which is shown in FIG. 2. FIG. 1 is a histology photograph of an epididymal section from a control animal. As shown in FIG. 1, the ductuli efferentes in the epididymides were lined by a tall columnar epithelium and all tubules contained sperm. The average diameter of the lumen of the ductuli efferentes was approximately 100–125 microns. The coils of the ductus epididymis in the epididymides were lined by a tall pseudostratified epithelium and all coils contained sperm. The average diameter of the lumen of the coils of the ductus epididymis was approximately 250 microns. The lining epithelium of the ductus epididymis varied little in height from head to tail. The epithelium lining the ductus deferens was a low columnar epithelium. The average diameter of the coils in the ductus deferens was approximately 400 microns. All coils of the ductus deferens contained sperm.

In the treated animals, on gross observation the epididymis was approximately normal size. As shown in FIG. 2, the ductuli efferentes were lined by a tall columnar epithelium and did not contain any sperm. There was an increase in the interductal connective tissue. The average lumen diameter was approximately 50 microns. The coils of the ductus epididymis were lined by a tall pseudostratified epithelium. None of the coils of the ductus epididymis contained sperm. All of the coils contained amorphous pink secretory material. There was an increase in the intercoil connective tissue in all parts of the epididymis. The epithelium increased in height in the coils of the epididymis from the head to the tail. The ductus deferens was lined by a low columnar epithelium. None of the coils of the ductus deferens contained sperm. Its diameter was 200 microns. All of

the coils contained amorphous pink material or necrotic debris.

Until recently, the epididymis was considered a passive channel through which the spermatozoa could leave the seminiferous tubules in order to be stored before being ejaculated. Recently, it has been recognized that during the time of their passage though the epididymis the spermatozoa change from functionally immature cells unable to fertilize an egg to cells with full fertilizing capacity, thus achieving complete maturation, and therefore that the epididymis has a crucial role in the physiology of male reproduction. This observation has focused interest on the epididymis as a possible target for pharmacological male contraception.

The process of sperm maturation requires a cooperative interaction between the sperm and the epididymal epithelium. The morphological and biochemical modifications occurring in the spermatozoa seem to be mediated by secretory products of the epididymis. A number of epididymal secretory glycoproteins have been identified in the epididymal tissue and fluid of the rat, rabbit, hamster and bull. The protein synthesis in the epididymis shows regional differences, which parallel the morphological changes occurring in the luminal sperm. The greatest activity of the protein synthesis machinery is present in the initial segment, i.e. head or caput, of the epididymis, where the spermatozoa undergo the most dramatic morphological and biochemical changes. After being produced in the caput segment of the epididymis, these proteins interact with and remain attached to spermatozoa as the cells are transported along the duct.

Histochemistry which was done on treated rats in a follow-up indicated that the glycoprotein coating the sperm had been significantly decreased as compared to the control thus inhibiting sperm maturation which is necessary in order for sperm to penetrate and fertilize an egg. Hence the method described in this example achieves male sterilization without affecting spermatogenesis and hormone (testosterone) production in the testes.

EXAMPLE 3

Twenty-one sexually mature mixed breed dogs having ejaculate containing 150 million/ml to 200 million/ml sperm were divided into three groups:

1. Control dogs
2. Dogs injected intratesticularly with 1.5 ml of 0.1 M (5%) Zinc Gluconate and 0.1 M (1.74%) Arginine neutralized with Hydrochloric Acid to pH 7.0
3. Dogs injected into the caudal epididymis with 0.5 ml of 0.1 M (5%) Zinc Gluconate and 0.1M (1.74%) Arginine neutralized with Hydrochloric Acid to pH 7.0.

After injection, the dogs acted and ate normally. One week after treatment, sperm motility was zero and the sperm was broken. Four semen collections performed during a three-month period after treatment revealed the following:

Group 2. In four animals, no fluid was obtained and the animals were dry. Three animals had 1 ml of ejaculate or less and no sperm were found in the ejaculate. Collectively, these results are an indication of the drying effect on the prostate and fluid and on the suppression of spermatogenesis.

Group 3. All animals ejaculated fluid but there were no sperm, only cell debris. This is an indication that the route of administration affects maturation of sperm without affecting testosterone level and the prostate.

When zinc tannate was used in place of neutralized zinc gluconate with arginine, the dogs had to be restrained with foam collars to prevent them from licking and biting their testicles. Sperm condition after treatment was like that reported with neutralized zinc gluconate with arginine but the animals suffered more pain or discomfort.

EXAMPLE 4

Zinc tannate is a proven chemical sterilant when it is injected into the testis of bulls (U.S. Pat. Nos. 4,156,427 and 4,339,438). Animals treated with zinc tannate have difficulty walking for about twenty-four hours after treatment and solutions of zinc tannate are not stable to heat and light under ambient conditions for more than about six months. These facts have limited the marketability of zinc tannate as a chemical sterilant.

In work reported in Example 1, the combination of neutralized zinc gluconate with arginine was demonstrated as very effective at decreasing the size of the reproductive organs. The experiment which is reported in this example was conducted to determine whether the combination of neutralized zinc gluconate with arginine is as effective as zinc tannate at inhibiting spermatogenesis and whether animals treated with the combination experience less morbidity.

For this example, twenty weaned bulls weighing about 500 lbs each were divided into four groups:

1. Control bulls
2. Bulls castrated with a knife
3. Bulls injected intratesticularly with 5-7 ml of Zinc Tannate (9%), pH 3.5
4. Bulls injected intratesticularly with 5-7 ml of 0.2M (10%) Zinc Gluconate and 0.2M (3.48%) Arginine neutralized with Hydrochloric Acid to pH 7.0

Before treatment, the body weight of each bull was determined, a blood sample taken and the testis circumference measured. For the purpose of following their reaction, the animals were marked with different colored ear tags. The bulls in Group 1 were given orange ear tags, Group 2 were marked with brown ear tags, Group 3 with green tags and Group 4 with yellow tags.

The animals with yellow ear tags (Group 4) were the first to show some discomfort after treatment by lying down, stretching and walking somewhat spraddle legged indicating that the sterilant permeated faster than the sterilant in Group 3. This activity began 30 minutes to 1 hour after injection but by 6-8 hours after injection the animals had only slight difficulty in walking.

The same type of reaction but much more severe began in the animals with green tags approximately 45 minutes to 1 hour later than the animals with yellow tags. All of the animals in Group 3 walked with a stilted gait that extended to 24 hours in two animals and 48 hours in three animals.

When observed at 24 hours after treatment, the swelling of the animals with yellow tags was about ⅞ of that of the animals with green tags and their pain response was ½ to ⅞ that of the green. The animals in both groups recovered after 2 days and no abnormality was observed in their feeding behavior throughout the treatment.

Four months after treatment, the control animals had 150 million/ml to 280 million/ml sperm. The animals in the treatment groups had zero sperm. These results

indicate that neutralized zinc gluconate with arginine is as effective as zinc tannate as a chemical sterilant. It has several advantages over zinc tannate, however, because it significantly reduces the morbidity and reaction of the animals to the injection. In addition, solutions of neutralized zinc gluconate with arginine are stable over extended periods of time and can even be autoclaved.

EXAMPLE 5

Various solutions as shown in the following table were tested for effectiveness as a spermicide. Human males participating in this study were fertile semen donors selected after appropriate screening. One specimen from each of three males was used in this study. Specimens were collected by masturbation following three days abstinence. Following collection, specimens were incubated at 37 degrees C. for 15-30 minutes to allow for liquefaction. Semen volume, sperm density and motility percentage were assessed using a light microscope and a Makler Chamber (Jequier, A. and Crich, J.: Sperm count and assessment of sperm movements. In: *Semen Analysis—A Practical Guide*, A. Jequier and J. Crich, Eds., The Alden Press, Great Britain, 1986, p. 50). Motility of sperm were graded based on forward progression and a scale of 1+ (slowest) to 4+ (fastest).

For the data reported below, refrigerated spermicide solutions were kept at room temperature for 15 minutes to reach the same temperature as semen. An equal volume (0.5 ml) of semen and spermicide were mixed and this was considered 0 time.

EFFECT OF SPERMICIDAL SOLUTIONS ON SPERM MOTILITY

Solutions	pH	Male #	Initial Motility and Grade	1 Minute	10 Minutes	30 Minutes
2% Zinc Acetate	7.00	1	74% 3+	0%	0%	0%
		2	85% 3+	0%	0%	0%
		3	78% 3+	0%	0%	0%
2% Calcium Acetate	7.00	1	75% 3+	0%	0%	0%
		2	80% 3+	0%	0%	0%
		3	85% 4+	0%	0%	0%
2% Zinc Gluconate	7.00	1	74% 3+	0%	0%	0%
pH adjusted to		2	85% 3+	0%	0%	0%
7.00 with 5.0 N NaOH		3	78% 3+	0%	0%	0%
2% Zinc Gluconate	5.62	1	65% 3+	29% 2+	20% 1+	15% 1+
		2	75% 4+	35% 2+	28% 1+	20% 1+
		3	70% 3+	28% 2+	22% 1+	18% 1+

From the above, it is seen that zinc gluconate adjusted to pH 7.0 with sodium hydroxide is as effective as zinc acetate and calcium acetate as a spermicide while having the advantage of being neutral and therefore useful as a vaginal contraceptive. It is also seen that zinc gluconate in its acidic form is not as effective as when it is neutralized to pH 7.0. In addition, zinc gluconate in its acidic form does not meet the criteria for spermicidal agents recognized internationally which require the pH of the spermicide to be between 6.0 and 7.5 in order to be effective since the vagina is acidic while the pH of sperm is alkaline or neutral.

As various changes could be made in the above methods and products without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

What is claimed:

1. A method of inhibiting generation, maturation, motility or viability of sperm in a reproductive tract of an animal comprising applying in said reproductive tract an aqueous solution of a mineral gluconate salt and an amino acid capable of forming the solution, said aqueous solution neutralized to a pH in the range of 6.0 to 7.5 and applied in an amount effective to inhibit generation, maturation, motility or viability of sperm in the reproductive tract and said mineral gluconate salt and said amino acid being present in substantially equal molar amounts at a concentration in the range from about 0.05 M to about 2.0 M.

2. The method of claim **1** wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.05 M to about 0.3 M.

3. The method of claim **1** wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.1 M to about 0.2 M.

4. The method of claim **1** wherein the mineral gluconate salt is zinc gluconate.

5. The method of claim **4** wherein the amino acid is a basic amino acid selected from the group consisting of lysine, arginine, histidine and mixtures thereof.

6. A method of inhibiting generation or maturation of sperm in a testis or epididymis of a male animal comprising applying in said testis or epididymis an aqueous solution of zinc gluconate and an amino acid capable of forming the solution, said aqueous solution neutralized to a pH in the range of 6.0 to 7.5 and applied in an amount effective to inhibit generation or maturation of sperm in the testis or epididymis and said zinc gluconate and said amino acid being present in substantially equal molar amounts at a concentration in the range from about 0.05 M to about 2.0 M.

7. The method of claim **6** wherein the concentration of the zinc gluconate and the amino acid is from about 0.05 M to about 0.3 M.

8. The method of claim **6** wherein the concentration of the zinc gluconate and the amino acid is from about 0.1 M to about 0.2 M.

9. The method of claim **6** wherein the amino acid is a basic amino acid selected from the group consisting of lysine, arginine, histidine and mixtures thereof.

10. The method of claim **9** wherein the basic amino acid is arginine.

11. A method of inhibiting motility or viability of sperm in a vagina, cervix, uterus or fallopian tube of a female animal comprising applying in said vagina, cervix, uterus or fallopian tube an aqueous solution of a mineral gluconate salt and an amino acid capable of forming the solution, said aqueous solution neutralized to a pH in the range 6.0 to 7.5 and applied in an amount

effective to inhibit motility or viability of sperm in said vagina, cervix, uterus or fallopian tube and said mineral gluconate salt and said amino acid being present in substantially equal molar amounts at a concentration in the range from about 0.05 M to about 2.0 M.

12. The method of claim 11 wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.05 M to about 0.3 M.

13. The method of claim 11 wherein the concentration of the mineral gluconate salt and the amino acid is from about 0.1 M to about 0.2 M.

14. The method of claim 11 wherein the mineral gluconate salt is zinc gluconate.

15. The method of claim 14 wherein the amino acid is a basic amino acid selected from the group consisting of lysine, arginine, histidine and mixtures thereof.

* * * * *

APPENDIX D

In the Matter of Mostafa S. Fahim
Patent No. 5,070,080 File FMS 9122.1

The following has been received by the U. S. Patent and Trademark Office on the date stamped hereon: Maintenance Fee Transmittal Form and check for $1,575.00.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

002147

M75N8

GRACE J FISHEL
11970 BORMAN DRIVE
SUITE 220
ST. LOUIS MO 63146

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.
If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,070,080	284	950	----	07/303,747	12/03/91	01/30/89	08	YES	PAID

ITM NBR	ATTY DKT NUMBER
1	91221

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
002147

75M7/1005

GRACE J. FISHEL
THE SECURITY PLAZA BUILDING
SUITE 100
929 FEE FEE ROAD
ST. LOUIS, MO 63043

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,070,080	283	480	----	07/303,747	12/03/91	01/30/89	04	YES	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	91221

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COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

APPENDIX E

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MAY 09, 2003

PTAS

GRACE J. FISHEL
11970 BORMAN DRIVE
SUITE 220
ST. LOUIS, MO 63146

700030095A

700030095A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/09/2003

REEL/FRAME: 013634/0511
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
FAHIM, MOSTAFA S.

DOC DATE: 09/27/1989

ASSIGNEE:
TECHNOLOGY TRANSFER, INC.
33 E. BROADWAY
SUITE 190
COLUMBIA, MISSOURI 65203-4290

SERIAL NUMBER: 05757099
PATENT NUMBER: 4156427

FILING DATE: 01/05/1977
ISSUE DATE: 05/29/1979

SERIAL NUMBER: 06042550
PATENT NUMBER: 4339438

FILING DATE: 05/25/1979
ISSUE DATE: 07/13/1982

SERIAL NUMBER: 07230582
PATENT NUMBER: 4937234

FILING DATE: 08/10/1988
ISSUE DATE: 06/26/1990

SERIAL NUMBER: 07303747
PATENT NUMBER: 5070080

FILING DATE: 01/30/1989
ISSUE DATE: 12/03/1991

013634/0511 PAGE 2

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

ASSIGNMENT AND AGREEMENT

FOR VALUE RECEIVED, **MOSTAFA S. FAHIM** does hereby sell, assign, and transfer to **TECHNOLOGY TRANSFER, INC.**, a Missouri corporation, with registered agent and address of David L. Knight, 609 E. Walnut, Columbia, Missouri, 65201, and said corporation's successors and assigns, his entire right, title, and interest, for all countries, in and to certain inventions relating to Kastrin and the chemical sterilization of male pet animals (dogs and cats) described in application for Letters Patent of the United States Serial Number 4,156,427; United States Serial Number 4,339,438; United States Patent Application No. 230,582 dated 08/10/88 (Minerals in Bioavailable Form); and United States Patent Application No. 303,747 dated 01/30/89 (Method of Inhibiting Generation, Maturation, Motility and Viability of Sperm with Minerals in Bioavailable Form and Compositions Useful Therefor); and all rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all letters patents which may be granted therefor, and under any and all extensions, divisions, reissues and continuations of said letters patents, related to pet animals (dogs and cats).

Executed at Columbia, Missouri, this 27th day of September, 1989.

Mostafa S. Fahim

MOSTAFA S. FAHIM

STATE OF MISSOURI)
) ss.
COUNTY OF BOONE)

On this 27th day of September, 1989, before me personally appeared Mostafa S. Fahim, to me known to be the person described in and who executed the foregoing instrument, and acknowledged that he executed the same as his free act and deed.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed my official seal, at my office in Columbia, Missouri the day and year first above written.

Anna K. Davis

NOTARY PUBLIC

My commission expires: October 2, 1991.

APPENDIX F

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MAY 13, 2003

PTAS

GRACE J. FISHEL
11970 BORMAN DR.
STE. 220
ST. LOUIS, MO 63146

700030326A

700030326A

UNITED STATES PATENT AND TRADEMARK OFFICE
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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/13/2003

REEL/FRAME: 013645/0252
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
FAHIM, MOSTAFA S.

DOC DATE: 05/12/2003

ASSIGNEE:
FAHIM, ZUHAL
1634 MARSHALL
HOUSTON, TEXAS 77006-4122

SERIAL NUMBER: 07230582
PATENT NUMBER: 4937234

FILING DATE: 08/10/1988
ISSUE DATE: 06/26/1990

SERIAL NUMBER: 07303747
PATENT NUMBER: 5070080

FILING DATE: 01/30/1989
ISSUE DATE: 12/03/1991

VIOLET MCCOY, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

ASSIGNMENT

WHEREAS, MOSTAFA S. FAHIM, who died on December 7, 1995, late a citizen of the United States and a resident of the county of Boone, Missouri, during his lifetime invented certain new and useful improvements and filed the following patent applications which issued as U.S. patents:

U.S. application serial No. 230,582, filed August 10, 1988, for MINERALS IN BIOAVAILABLE FORM which issued as U.S. patent No. 4,937,234 on June 26, 1990; and,

U.S. application serial No. 303,747, filed January 30, 1989, for METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM which issued as U.S. patent No. 5,070,080 on December 3, 1991;

WHEREAS, MOSTAFA S. FAHIM executed an ASSIGNMENT AND AGREEMENT dated September 27, 1989 assigning a partial interest in the aforementioned patents then pending as patent applications to TECHNOLOGY TRANSFER, INC. in the field of chemical sterilization of male pet animals (dogs and cats), retaining all right title, title and interest to the remainder of said patents;

WHEREAS, I, ZUHAL FAHIM, am the Personal Representative of MOSTAFA S. FAHIM by Letters of Administration issued July 3, 1996 by the Circuit Court of Boone County, Missouri, Probate Division and am the sole and exclusive owner of the remainder of said patents; and,

WHEREAS, I, ZUHAL FAHIM, an individual, am desirous of acquiring the entire right, title and interest in and to the aforesaid inventions and patents subject to the partial assignment to TECHNOLOGY TRANSFER, INC.

NOW THEREFORE, I, ZUHAL FAHIM acting as Personal Representative of MOSTAFA S. FAHIM do hereby assign and transfer for value received to ZUHAL FAHIM, an individual, residing at 1634 Marshall, Houston, Texas 77006-4122, her successors and assigns the entire right, title and interest in U.S. patent Nos. 4,937,234 and 5,070,080, including any and all extensions, divisions, reissues and continuations of said patents, subject to the ASSIGNMENT AND AGREEMENT dated September 27, 1989 assigning a partial interest in the aforementioned patents.

Executed at Houston, Texas, this 12 day of May, 2003.

Zuhal Fahim

ZUHAL FAHIM, acting as
Personal Representative of
MOSTAFA S. FAHIM

STATE OF TEXAS)
) ss.
COUNTY OF Harris)

On this 12 day of May, 2003, before me personally appeared ZUHAL FAHIM, who acknowledged that she executed the above assignment of her own free will and for the purpose therein set forth.

Notary Public

My commission expires: 6-26-2004

ESTEBAN GONZALEZ
Notary Public
STATE OF TEXAS
My Comm. Exp. 06-26-2004

APPENDIX G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

INAD-8349

November 14, 1991

Mostafa S. Fahim, Ph.D.
111 Allton Building
School of Medicine
University of Medicine
Columbia, Missouri 65212

Dear Dr. Fahim:

We acknowledge receipt of your submission dated November 7, 1991 for the investigational use of neutralized zinc arginine in dogs.

Your submission has been assigned INAD number 8349 and has been forwarded to the proper reviewer for consideration.

Please refer to this number when submitting any future correspondence pertaining to the use of the aforementioned drug.

This is not an authorization letter.

Sincerely,

Stephen L. Henry

Stephen L. Henry, Supervisor
Document Control Staff
Center for Veterinary Medicine
HFV-199

APPENDIX H

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NADA 141-217 A0000

MAR 17 2003

Zuhal Fahim
President, Technology Transfer, Inc.
Research Associate
Center of Reproductive Science and Technology
111 Allton Building, School of Medicine
University of Missouri-Columbia
Columbia, Missouri 65212

Dear Mrs. Fahim:

In an original New Animal Drug Application (NADA) dated February 10, 2003, (A0000) you requested approval of Neutersol® (zinc gluconate neutralized by arginine) Injectable Solution for chemical sterilization in 3 to 10 month old male dogs.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. Prior to distribution and marketing, three copies of each component of the final printed labeling must be submitted to CVM. This labeling should be identical to the facsimile labeling submitted on February 10, 2003, (A0000).

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

FDA may take regulatory action if any drug products are shipped prior to completion of the validation process. See our letter dated January 14, 2003 (INAD 8349 P0071). An expiration dating of 24 months is acceptable for this product.

If you submit any correspondence in the future relating to this approval, you should include a citation to this letter by date and NADA number. Any request to change the conditions of approval may require the submission of a supplemental application. If you have any questions, please contact Dr. Melanie Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely yours,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure: FOI Summary

APPENDIX I

DILIGENCE LISTING FOR INAD 8349

TECHNOLOGY TRANSFER, INC. (TTI) **CENTER FOR VETERINARY MEDICINE (CVM)**

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
07-24-91 (A000)	TTI submits a request for assignment of INAD number to use zinc gluconate neutralized by arginine as a chemical sterilant for male pet animals		
08-29-91 (C001)	TTI submits a plan of action and protocols for dose titration and target animal safety studies in male puppies and cats		
		09-24-91	William H. Taylor, Investigator, FDA, Kansas City, Missouri, visits and notes no objectionable conditions or practices during the inspection
11-07-91 (C002)	TTI submits preliminary puppy data in support of planned dose titration, target animal safety, and clinical trial in male puppies	11-14-91	CVM acknowledges the 11/7/91 submission (C002) and assigns INAD number 8349 for investigational use in male dogs and cats
		02-19-92	CVM acknowledges the 7/24/91 submission (A000), comments on the 8/29/91 submission of dose titration and target animal safety protocols (C001), and requests two copies of investigational labeling
03-06-92 (C005)	TTI submits two copies of revised investigational labels		
03-23-92 (C007)	TTI requests priority review status in the INAD stage	03-23-92	CVM comments on the 11/7/91 submission of preliminary puppy data (C002)
05-11-92 (C008)	TTI submits preliminary data in support of a dose titration study in male cats which is currently underway		
05-14-92 (C009)	TTI submits a video depicting intratesticular injection of male cats and subsequent recovery		
		06-19-92	CVM comments on and requests revision of the investigational labels submitted 3/6/92 (C005)
07-16-92	TTI submits two copies of revised investigational labels In response to CVM's letter of 6/19/92 regarding the 3/6/92 submission of labels (C005)		
07-17-92 (C011)	TTI submits a response to items A.8. and A.10 of CVM's letter of 2/19/92 regarding the 7/24/91 submission (A000) and 8/29/91 submission of protocols for dose titration and target animal safety studies in male puppies and cats (C001)		
08-10-92 (C012)	TTI submits a response to CVM's letter of 3/23/92 regarding the 11/7/91 submission of preliminary puppy data		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
	(C002)		
		08-21-92	CVM classifies zinc gluconate neutralized by arginine as Type 1D according to CVM's Expedited Review Guideline, i.e., the drug is a new molecular entity but appears to have decreased safety compared with the alternative therapy (surgical castration) and denies TTI's 3/23/92 request for expedited review status (C007)
10-22-92 (C013)	TTI submits a response to CVM's letter of 2/19/92 regarding the 7/24/91 submission (A000) and 8/29/91 submission of protocols for dose titration and target animal safety studies in male puppies and cats (C001)		
11-18-92 (C014)	TTI submits a proposed protocol for conducting a clinical trial in puppies		
		12-24-92	CVM comments on the 5/11/92 submission of preliminary cat data (C008) and 5/14/92 submission of a video depicting injection of cats (C009)
		12-24-92	CVM comments on the 7/17/92 submission of the response to two items in CVM's letter of 2/19/92 (C011)
		03-31-93	CVM comments on the 8/10/92 submission (C012) in response to CVM's letter of 3/23/92 regarding the 11/7/91 submission of preliminary puppy data (C002)
		05-14-93	CVM comments on the 11/18/92 submission of a proposed protocol for a clinical trial in puppies (C014)
07-12-93 (P0015)	TTI submits a report regarding points for consideration which provides a summary of the physiological and pharmacological effects of zinc to substantiate the efficacy and safety of zinc gluconate neutralized by arginine and which comments on issues raised by CVM in previous correspondence		
07-12-93 (P0016)	TTI submits a report on the dose titration study in puppies, inclusive of Day 0 through 12 months post-injection data (Protocol 1: Neutralized Zinc Arginine/ Puppies/Efficacy/Titration/Reproduction		
07-12-93 (P0017)	TTI submits a report on the target animal safety study in puppies (Protocol 2: Neutralized Zinc Arginine/ Puppies/Toxicity/Target Animal Safety)		
10-19-93 (H0018)	TTI submits a response to CVM's letter of 8/21/92 which denied expedited review status (C007) and requests reconsideration of granting expedited review status		
10-19-93	TTI submits a response to CVM's letter		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
(H0019)	of 3/31/93 regarding the 8/10/92 submission (C012) which was in response to CVM's letter of 3/23/92 regarding the 11/7/91 submission of preliminary puppy data (C002)		
12-03-93 (H0020)	TTI submits a response to CVM's letter of 5/14/93 regarding the 11/18/92 submission of a proposed protocol for a clinical trial in puppies (C014) and requests a meeting to discuss the overall status of the investigational drug		
12-13-93	TTI requests a meeting with CVM regarding the status of review of dose titration and target animal safety reports	12-17-93	CVM telephones regarding proposed dates for the meeting
		01-05-94	CVM acknowledges the 7/12/93 submission of points for consideration (P0015) and indicates the following are currently under veterinary medical review: (1) C013 dated 10/22/92 [response to CVM's letter of 2/19/92 regarding the 7/24/91 submission (A000) and 8/29/91 submission of protocols for dose titration and target animal safety studies in puppies and cats (C001)), (2) P0016 dated 7/12/93 (puppy dose titration report), (3) P0017 dated 7/12/93 (puppy target animal safety report), and (4) H0019 dated 10/19/93 [response to CVM's letter of 3/31/93 regarding the 8/10/92 submission (C012) in response to CVM's letter of 3/23/92 regarding the 11/7/91 submission of preliminary data in puppies (C002)]
		02-03-94	In response to the 10/22/92 submission (C013) which was in response to CVM's letter of 2/19/92 regarding the 7/24/91 and 8/29/91 submissions of dose titration and target animal safety protocols (A000, C001), CVM comments on the statistical considerations but does not review the veterinary medical aspects of the protocols
		02-16-94	CVM telephones to schedule a meeting and to indicate CVM's two areas of concern--(1) determination of the dose scale, and (2) margin of safety
		02-25-94	In response to the 10/19/93 submission (H0019) which was in response to CVM's letter of 3/31/93 regarding the 8/10/92 submission (C012) in response to CVM's letter of 3/23/92 re-

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
			garding the 11/7/91 submission of preliminary puppy data (C002), CVM accepts the preliminary study data as corroborative data in support of an eventual New Animal Drug Application, reiterates two safety concerns, and indicates no formal response to CVM's comments is required
03-31-94	TTI meets with CVM to discuss CVM's two safety concerns	03-31-94	CVM states it will use the information supplied by TTI at the meeting to complete review of the dose titration and target animal safety studies and will include a recommendation regarding when TTI can commence with the clinical trial
04-20-94 (G0028)	As requested during the 3/31/94 meeting with CVM, TTI submits revised proposed labeling (package insert, vial label, carton label)		
04-28-94 (Y0029)	TTI submits minutes of 3/31/94 meeting and requests expedited review status	06-06-94	CVM responds to the 4/28/94 submission (Y0029) indicating the minutes accurately reflect the 3/31/94 discussion, encloses CVM's minutes, and indicates current review of the request for expedited review status [10/19/93 (H0018)]
		06-07-94	CVM telephones regarding questions and points of confusion in review of the dose titration study (P0016) and target animal safety study (P0017)
06-21-94 (H0035)	TTI submits additional safety data in response to CVM's 6/7/94 telephone call		
07-08-94 (Y0033)	TTI submits confirmation of points discussed by telephone with CVM's statistician regarding significance level for variables involved in the dose titration study in puppies		
08-03-94 (P0034)	TTI submits a report of dose titration study in puppies, inclusive of data 13-24 months post-injection as a continuation of the Day 0 through 12 months post-injection data submitted on 7/12/93 (P0016)		
		08-19-94	CVM acknowledges and concurs with information presented in the 7/8/94 submission (Y0033) regarding statistical significance level for variables in the puppy dose titration study
		01-06-95	In response to the 10/19/93 submission requesting reconsideration of expedited review status (H0018), CVM denies expedited review status and again classifies zinc gluconate neutralized by arginine as a Type 1D compound according to the Center's

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
			Expedited Review Guideline
		02-02-95	CVM comments on the 7/12/93 submission of puppy dose titration data (P0016) and puppy target animal safety data (P0017), acknowledges the 6/21/94 submission of additional safety data (H0035), requests revised final reports for these studies, and recommends a limited field trial in animal shelters or humane societies
		02-28-95	In response to the 12/3/93 submission (H0020) in response to CVM's letter of 5/14/93 regarding a proposed clinical trial protocol submitted 11/18/92 (C014), CVM provides general comments and indicates a widespread clinical trial protocol can not be finalized until after a limited field trial is conducted
		02-28-95	In response to the 8/3/94 submission of puppy dose titration data through 24 months post-injection (P0034), CVM finds that the data demonstrate the effects of zinc gluconate neutralized by arginine persist for at least 24 months post-injection and indicates continuing concerns about the dosing scale and safety
		03-21-95	Carl J. Montgomery, Investigator, FDA, Lenexa, Kansas, visits and notes no objectionable conditions or practices during the inspection
07-10-95 (P0037)	TTI submits a response to CVM's letter of 2/2/95 regarding the 7/12/93 submissions of dose titration and target animal safety data (P0016, P0017) and the 6/21/94 submission of additional safety data (H0035), inclusive of excised testes raw data (as proposed in CVM's 2/2/95 letter) and revised proposed labeling		
08-02-95 (E0038)	TTI submits a revised proposed clinical trial protocol and requests a meeting with CVM to discuss the protocol		
09-22-95	Per CVM's telephone request on 9/20/95, TTI forwards a disk containing excised testes raw data and graph showing volume of injection vs. testis width as submitted on 7/10/95 (P0037)		
11-27-95	TTI submits a response to CVM's letter of 2/28/95 providing CVM's comments on the 8/3/94 submission of 13-24 month follow-up data on the puppy dose titration study (P0034)		
		12-15-95	CVM comments on the 8/2/95 submission of a revised proposed clinical trial

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
			protocol (E0038) and requests submission of a user/handler data package
		03-12-96	In response to the 7/10/95 submission (P0037) which was in response to CVM's letter of 2/2/95 regarding the 7/12/93 submissions of dose titration and target animal safety data (P0016 and P0017) and 6/21/94 submission of additional safety data (H0035), CVM comments on the proposed doses and indicates results of the field study will verify the safety of the dose ranges proposed in the clinical trial protocol
04-24-96 (E0042)	TTI submits a response to CVM's letter of 12/15/95 and a revised proposed clinical trial protocol		
04-24-96 (H0041)	TTI submits a response to CVM's letter of 3/12/96 providing CVM's comments on the 7/10/95 submission (P0037)		
08-01-96 through 10-31-96	TTI telephones CVM several times to inquire about the status of review of the revised proposed clinical trial protocol (E0042)		
		11-06-96	CVM telephones to indicate the Acceptance letter had been sent to TTI on 7/12/96 and faxes a copy of the letter to TTI; CVM's response indicates (1) the issues raised in CVM's letters of 12/15/95 and 3/12/96 have been satisfactorily addressed and (2) CVM's acceptance of the proposed clinical trial protocol
12-03-96	TTI submits certification that TTI did not and will not use any person debarred under subsections (a) or (b) of Section 306(k) of the U.S. Food, Drug & Cosmetic Act		
12-03-96	TTI submits a letter from Aaron Industries, Inc., Clinton, South Carolina, granting permission to CVM to reference Drug Master File (DMF) #11903 for zinc gluconate in support of INAD 8349		
07-18-97 (P0043)	TTI submits the Manufacturing Chemistry: Methods and Controls (CMC) report and an abbreviated Environmental Assessment (EA)		
10-07-97 (H0044)	TTI submits a request to the Division of Manufacturing Technologies to waive an Environmental Assessment (EA) and grant categorical exclusion		
11-19-97	TTI submits notification of initiation of the clinical trial at Site 1 on 11/13/97 and Notice of Drug Shipment of 80 vials to Site 1		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
		01-28-98	In response to the 10/7/97 submission (H0044), CVM agrees to categorical exclusion from an Environmental Assessment (EA), therefore, a review of the abbreviated EA is not necessary and the environmental technical component for the product is complete and comments to include a copy of this letter in the NADA with assurances there is no new information available when the NADA is submitted
		02-09-98	In response to the 7/18/97 Manufacturing Chemistry: Methods and Controls (CMC) submission (P0043), CVM indicates the phased component is incomplete, comments on several deficiencies, i.e., the DMF for bulk zinc gluconate is deficient and the DMF holder has been notified by letter
07-27-98	TTI submits notification of proceeding with the clinical trial at a second site on 8/3/98 in view of no adverse reactions at Site 1 (initiated 11/13/97) and Notice of Drug Shipment of 80 vials to Site 2		
08-21-98	TTI submits notification of proceeding with the clinical trial at a third site on 8/24/98 in view of no adverse reactions at Site 2 (initiated 8/3/98) and Notice of Drug Shipment of 80 vials to Site 3		
10-30-98	TTI submits notification of no serious adverse reactions to date in 45 puppies injected at Site 3, 35 puppies injected at Site 1, and 6 puppies injected at Site 2; and Notice of Drug Shipment of an additional 20 vials to Site 3		
02-03-99	TTI submits notification of no serious adverse reactions to date in 72 puppies injected at Site 3, 49 puppies injected at Site 1, and 6 puppies injected at Site 2 and Notice of Drug Shipment of an additional 25 vials to Site 3		
		05-24-99 through 05-25-99	Jose R. Rodriguez, Investigator, FDA, Maitland, Florida, visits Site 3 and notes no objectionable conditions or practices during the inspection
06-02-99	TTI requests a meeting with CVM to discuss the trial currently underway and the possibility of amending various sections of the clinical trial protocol	06-11-99	CVM telephones to schedule a meeting with CVM on 7/7/99
07-07-99	TTI meets with CVM to discuss the current trial and reaches agreement on amending several sections of the clinical trial protocol (see 9/16/99)		
07-14-99 (Y0052)	TTI submits memorandum of the 7/7/99 meeting with CVM and requests a copy of CVM's memorandum of the meeting		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
08-05-99	Per CVM's request at the meeting on 7/7/99, TTI submits references from scientific literature regarding canine reproduction and fertility/infertility		
		09-16-99	In response to the 7/14/99 submission (Y0052), CVM confirms that TTI's minutes accurately reflect the discussions of 7/7/99 with CVM and encloses a copy of CVM's minutes which indicate the data collected to date can be considered pivotal data, the trial can be expanded to additional sites, the sites do not need to follow GLP guidelines, the age range can be increased to 12 months, the data can be pooled from multiple clinical sites, complete blood counts will not be required for the expanded sites, and the follow-up period can be shortened from one year to 6 months unless the dog has sperm at 6 months in which case follow-up will continue for 10 months
10-08-99	TTI submits notification of no serious adverse reactions in 218 puppies injected to date (three sites), initiation of the clinical trial at a fourth site on 10/11/99, and Notice of Drug Shipment of 20 vials to Site 4		
10-13-99	TTI submits original clinical trial protocol and amendments per discussion and agreement at the meeting with CVM on 7/7/99		
		11-12-99	CVM telephones to request that the clinical trial protocol be re-written to incorporate the amendments agreed upon at the meeting with CVM on 7/7/99
11-17-99	Per CVM's request, TTI submits the clinical trial protocol rewritten to incorporate the amendments agreed upon at the meeting with CVM on 7/7/99		
11-19-99	TTI submits notification of initiation of the clinical trial at a fifth site on 11/23/99 and Notice of Drug Shipment of 20 vials to Site 5		
11-29-99	TTI submits notification of change in the clinical investigator at Site 2		
01-13-00	TTI submits scientific publications as follows regarding aggressive behavior and prostate cancer in castrated dogs-- (1) Copulatory and Aggressive Behavior in the Prepuberally Castrated Dog, Hormones and Behavior 1:127-136, 1970; and (2) Prostatic Adenocarcinoma in a Castrated Dog, JAVMA 186(1):78-		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
	80, 1985		
07-26-00	TTI submits notification of an additional clinical investigator at Site 2		
09-15-00	TTI submits notification that an additional veterinarian is assisting the clinical investigator at Site 1		
02-01-01	TTI's statistical consultant telephones CVM's statistician regarding how to handle the discordant doses for 22 of the 268 study dogs and the one .25/.25 dosed dog	03-02-01	CVM telephones indicating it is agreeable to CVM's statistician and primary reviewer to group the 22 discordant-dosed dogs in the lower dose group (for safety reasons as was explained by TTI) and that the 0.25 mL dosed dog is a deviation and his data should be included in the safety statistics while excluded from the efficacy statistics
06-05-01 (P0062)	TTI submits the Final Report: Clinical Safety and Efficacy Component [Protocol 5: Clinical Evaluation of a Single Intratesticular Injection of Zinc Gluconate Neutralized by Arginine (100 mg/mL) as a Chemical Sterilant in Male Puppies] and two disks containing files used in the statistical analyses		
06-13-01	TTI submits a request for categorical exclusion for preparation of an Environmental Assessment (EA) and declares no extraordinary circumstances exist which may significantly affect the human environment		
06-19-01 (P0064)	TTI submits a response to CVM's letter of 2/9/98 which raised questions regarding the Manufacturing Chemistry: Methods and Controls (CMC) submission of 7/18/97 (P0043)		
		07-09-01	In response to TTI's inquiry by telephone, CVM confirms receipt of the clinical trial submission
		12-04-01 through 12-07-01	Sandra L. Shire, Investigator, FDA, Irvine, California, visits Site 1 and notes no objectionable conditions or practices during the inspection
11-28-01	TTI contacts CVM regarding status of review of the clinical trial submission (P0062)	12-19-01	CVM acknowledges the long history and multiple reviewers involved and indicates CVM anticipates a completion date of mid-February for review of the clinical trial submission (P0062)
		02-14-02	CVM telephones regarding concern of the final reviewer about one dog injected at Site 2 and requests additional information
03-11-02	TTI submits a response addressing the concern of the final reviewer of the clinical trial submission with regard to a dog injected at Site 2		
		04-05-02	In response to the 6/19/01 submission (P0064) which was in response to

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
			CVM's letter of 2/9/98 regarding the 7/18/97 Chemical Manufacturing: Methods and Controls submission (P0043), CVM indicates the phased component is incomplete, indicates the deficiencies, and requests submission of the proposed vial labeling
05-14-02	TTI requests a meeting with CVM to discuss the data generated thus far in cats and to modify the current target animal safety study protocol for cats	05-30-02	CVM telephones to discuss dataset discrepancies in the 6/5/01 submission of the Final Report: Clinical Safety and Efficacy Component (P0062)], to set a date for the meeting requested by TTI, and to request a more detailed agenda; CVM faxes the data set discrepancies for comment and resolution
05-30-02	TTI telephones CVM regarding the discrepancies in the data set for the 6/5/01 submission of Final Report: Clinical Safety and Efficacy Component (P0062) and schedules a meeting with CVM on 7/11/02 to discuss the cat data		
06-05-02	TTI telephones to discuss the data set discrepanies with CVM's statistician and the final reviewer of the clinical trial submission (P0062) and faxes a table to CVM to resolve the discrepancies		
06-07-02	TTI submits a detailed agenda for the meeting with CVM on 7/11/02 relative to use of zinc gluconate neutralized by arginine in cats	06-07-02	CVM telephones to confirm the data set discrepancies were resolved and to indicate the acceptance letter regarding the 6/5/01 clinical trial submission (P0062) will be forwarded next week
		06-12-02	CVM telephones to cancel the meeting scheduled for 7/11//02 and suggests submission of substantial evidence for the doses proposed for cats and a target animal safety protocol for cats
06-12-02 (G0070)	TTI submits the Freedom of Information (FOI) summary for use of zinc gluconate neutralized by arginine as a sterility/infertility agent in male dogs and also submits it in electronic format		
		06-18-02	In response to the 6/5/01 submission of the Final Report: Clinical Safety and Efficacy Component (P0062), CVM indicates the effectiveness and safety technical sections are considered to be complete for the purpose of recommending approval of a New Animal Drug Application (NADA) and comments on product safety issues that should be addressed in the labeling
06-20-02	TTI submits a response to CVM's letter of 4/5/02 regarding the 6/19/01 Manufacturing Chemistry: Methods and Controls (CMC) submission (P0064)		
07-12-02	TTI submits the labeling technical sec-		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
(G0072)	tion (vial label, package insert, Client Information Sheet, carton label and one sample carton, one actual caliper, and one video showing injection procedure for male dogs)		
07-23-02	TTI contacts CVM regarding status of the 6/20/02 submission which was in response to CVM's letter of 4/5/02 regarding the Manufacturing Chemistry: Methods and Controls (CMC) submission of 6/19/01 (P0064)		
07-26-02	TTI submits names of individuals who are authorized to represent TTI in communications regarding INAD 8349	07-29-02	CVM requests submission of the labeling technical section in electronic format
07-29-02	TTI submits the vial label, package insert, Client Information Sheet, and carton label in electronic format		
		07-30-02	CVM confirms receipt of the 6/20/02 submission which was in response to CVM's letter of 4/5/02 regarding the 6/19/01 CMC submission (P0064) and indicates it is in the review queue with a due date of 12/13/02
07-30-02	The Drug Master File (DMF) holder submits an updated DMF 011-903 file for bulk zinc gluconate per CVM's letter of 4/5/02 in response to the CMC submission of 6/19/01 (P0064)		
		07-31-02	CVM telephones with a question about the video and indicates the Freedom of Information (FOI) summary and labeling are being reviewed simultaneously
08-20-02	TTI telephones to confirm receipt of the DMF update from the DMF holder	08-21-02	DMF staff confirms receipt of the DMF update
09-06-02	TTI requests a meeting with the Acting Director, Office of New Animal Drug Evaluation (ONADE), and CVM team members to discuss expediting review of submissions and specifically the 6/20/02 CMC submission (P0064)		
		10-02-02	CVM telephones to request a facsimile of the Material Safety Data Sheet (MSDS) and indicates (1) the FOI has been revised and is complete, (2) the package insert and Client Information Sheet (CIS) have been revised, (3) the vial label and carton label will need to be revised and resubmitted
10-02-02	TTI faxes the MSDS to CVM		
10-11-02	TTI meets with CVM and was informed: (1) the FOI and labeling components are currently under review and are incomplete; (2) TTI will receive CVM's comments by the end of 10/02 and may contact CVM to set up a meeting in 11/02 to discuss the comments, and (3)		

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
	the CMC submission will be reviewed in accordance with the queue policy but minor issues could be resolved by telephone or fax		
10-16-02	TTI telephones CVM to request the 11/02 meeting		
10-22-02	TTI submits Memorandum of Conference with CVM held 10/11/02	10-24-02	CVM telephones to schedule a meeting with TTI on 11/15/02; CVM faxes its Minutes from the 10/11/02 meeting (dated 10/15/02); see 10/11/02 entry
		10-29-02	In response to the 6/12/02 FOI submission (G0070), 7/12/02 labeling submission (G0072), and 7/26/02 submission listing individuals who TTI authorizes CVM to communicate with (G0073), CVM indicates the FOI is complete (as attached) and labeling is incomplete; attaches revised package insert and CIS; and outlines revisions to vial and carton labels and video
11-11-02 (Z0077)	TTI submits revised labeling components and FOI to facilitate discussion at the 11/15/02 meeting with CVM		
11-15-02	TTI meets with CVM to finalize the labeling technical section and FOI	11-15-02	CVM e-mails the revised package insert and CIS based on today's meeting
		12-10-02	CVM e-mails the final version of the FOI based on the 11/15/02 meeting, and indicates TTI will not need to resubmit the FOI
		12-13-02	Teleconference with CVM and Meridian Medical Technologies (the contract manufacturer) regarding all remaining Chemistry: Methods and Controls (CMC) issues (3 questions)
12-17-02	TTI submits Form FDA 2656 (Registration of Drug Establishment/Labeler Code Assignment) for initial registration		
12-19-02 (G0078)	TTI submits the revised labeling technical section (G0072)		
12-23-02 (P0071)	TTI submits responses to the 3 questions concerning the CMC submission as an amendment to the 6/20/02 CMC submission	12-23-02	In response to the 11/11/02 submission (Z0077), CVM indicates it considers the FOI Summary technical section to be complete for the purpose of recommending approval of a New Animal Drug Application and encloses Minutes from the 11/15/02 meeting
		12-23-02	FDA assigns Drug Labeler Code 67647 to TTI
		01-14-03	In response to the 7/18/97 submission (P0043), as amended by the 6/19/01 submission (P0064), and 6/20/02 and 12/23/02 submissions (P0071), CVM Division of Manufacturing Technologies indicates it considers the CMC technical section to be complete for the

DATE	TTI ACTIVITY / RESPONSE	DATE	CVM ACTIVITY / RESPONSE
			purpose of recommending approval of a New Animal Drug Application
		02-06-03	In response to the 12/19/02 submission (G0078) of the final facsimile labeling, CVM indicates it considers the labeling technical section to be complete for the purpose of recommending approval of a New Animal Drug Application (NADA)
02-10-03 (A0000)	TTI submits an Administrative New Animal Drug Application (NADA)	02-13-03	CVM assigns NADA number 141-217 to the Administrative New Animal Drug Application
		03-17-03	In response to the 2/10/03 submission (A0000)) of the Administrative New Animal Drug Application (NADA), CVM Indicates approval of the NADA and 5 years of marketing exclusivity

APPENDIX J

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Technology Transfer, Inc.
Zuhal Fahim

Patent No.: 5,070,080

Issue Date: December 3, 1991

Patent Title: METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM

Mail Stop PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION

Sir:

The undersigned attorney hereby declares as follows:

1. THAT she is a patent attorney authorized to practice before the Patent and Trademark Office and has a Power of Attorney from the owner to act on behalf of the owner in this patent matter;

2. THAT she has reviewed and understands the contents of the application being submitted pursuant to 35 USC 156 and 37 CFR 1.740;

3. THAT she believes the patent is subject to extension pursuant to 35 USC 156 and 37 CFR 1.710;

4. THAT she believes an extension of the length claimed is fully justified under 35 USC 156 and the applicable regulations; and,

5. THAT she believes the patent for which the extension is being sought meets the conditions for extension of the term of patent as set forth in 35 USC 156 and 37 CFR 1.720.

The undersigned hereby declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief

are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Further declarant sayeth not.

Signed this 14th day of May, 2003.

Grace J. Fishel

5-16-03

DAC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Technology Transfer, Inc.
Zuhal Fahim

Patent No.: 5,070,080

Issue Date: December 3, 1991

Patent Title: METHOD OF INHIBITING GENERATION, MATURATION, MOTILITY AND VIABILITY OF SPERM WITH MINERALS IN BIOAVAILABLE FORM

Mail Stop PATENT EXTENSION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing is a complete application in duplicate for Patent Term Extension of United States Patent 5,070,080.

The filing fee is $1,120.00. A check in that amount is enclosed. In the event that additional fees are due, the Commissioner is authorized to charge the appropriate fee(s) to Deposit Account No. 06-1090.

Respectfully submitted,

(314) 878-0440

(Mrs.) Grace J. Fishel
Reg. No. 25,864

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Grace J. Fishel